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Assessment of cerebral blood flow autoregulation (CBF AR) with rheoencephalography (REG): studies in animals

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Abstract. The ability of cerebral vasculature to regulate cerebral blood flow (CBF) in the face of changes in arterial blood pressure (SAP) or intracranial pressure (ICP) is an important guard against secondary ischemia in acute brain injuries, and official guidelines recommend that therapeutic decisions be guided by continuous monitoring of CBF autoregulation (AR). The common method for CBF AR monitoring, which rests on real-time derivation of the correlation coefficient (PRx) between slow oscillations in SAP and ICP is, however, rarely used in clinical practice because it requires invasive ICP measurements. This study investigated whether the correlation coefficient between SAP and the pulsatile component of the non-invasive transcranial bioimpedance signal (rheoencephalography, REG) could be used to assess the state and lower limit of CBF AR. The results from pigs and rhesus macaques affirm the utility of REG; however, additional animal and clinical studies are warranted to assess selectivity of automatic REG-based evaluation of CBF AR.

1. Introduction

Brain injuries caused by vascular incidents or a physical trauma are a major public health concern worldwide [1]. In the United States alone, stroke and traumatic brain injury (TBI) annually account for 1.1 million hospitalizations, 200,000 deaths and $133 billion in medical costs [2, 3]. Moreover, 15 million Americans are permanently disabled because of the acquired brain damage [2]. Unfortunately, contemporary medicine can do little to remedy the direct damage caused by the primary vascular or traumatic insult, and the treatment focuses on maintenance of adequate cerebral blood flow (CBF) and prevention of the secondary ischemia in the hours and days following the primary injury.

Cerebral blood flow depends on systemic arterial blood pressure (SAP), intracranial pressure (ICP), and the cerebral vasculature, which continuously adjusts diameters of vessels in response to changes in cerebral perfusion pressure (CPP = SAP - ICP) [4]. The autoregulation (AR) of CBF keeps it constant for a wide range of CPP and protects the brain during transient episodes of hypo- or hypertension (**Figure** 1). Impairment of autoregulation, which often accompanies TBI or stroke, narrows the 'safe' range of CPP, and increases the risk of secondary ischemia even if the standards of care are strictly observed [4 - 6]. Treatment guidelines, therefore, recommend continuous monitoring of the state of CBF autoregulation and consideration of this information when making therapeutic decisions [7].

CBF AR is continuously assessed by correlating spontaneous slow (<0.05Hz) oscillations of SAP or CPP with related changes in cerebral blood volume (CBV): a negative correlation indicates

preserved autoregulation, whereas positive values suggest its impairment or loss [8]. As direct measurement of CBV with radiological methods is cumbersome, CBV fluctuations are usually assessed indirectly, through related changes in ICP. The correlation coefficient between SAP and ICP – called pressure-reactivity index (PRx) – has been established in clinical studies as a sensitive metric of CBF AR [4 – 6]. Its long-term monitoring (>30 minutes) allows for determination of the limits of autoregulation, defined as the range of SAP/CPP for which PRx is negative (**Figure** 2): this is an important piece of information, as SAP/CPP should, by all means, be kept within this range. Autoregulation is, unfortunately, rarely monitored in clinical practice because invasive ICP probes are not routinely implanted to patients with cerebrovascular pathologies. Noninvasive transcranial bioimpedance monitoring (rheoencephalography, REG) might, however, substitute ICP measurements, as REG also captures slow oscillations of cerebral intra-arterial volume caused by MAP changes. This study investigated whether the correlation coefficient between MAP and REG (called REGx) could be used to assess the reactivity of cerebral vasculature and determine the lower limit of CBF AR.

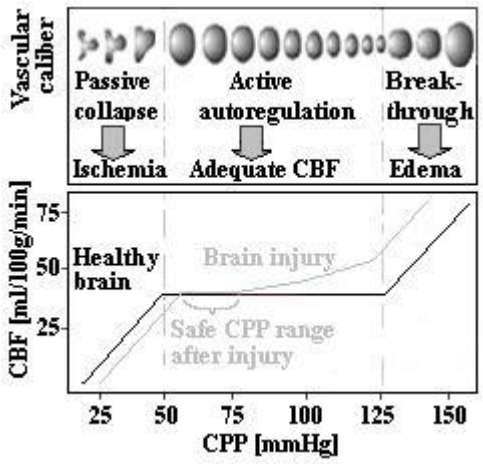

Figure 1. Schematic relationship between the cerebral perfusion pressure (CPP) and blood flow (CBF) in a healthy individual and a patient with an acute TBI or stroke.

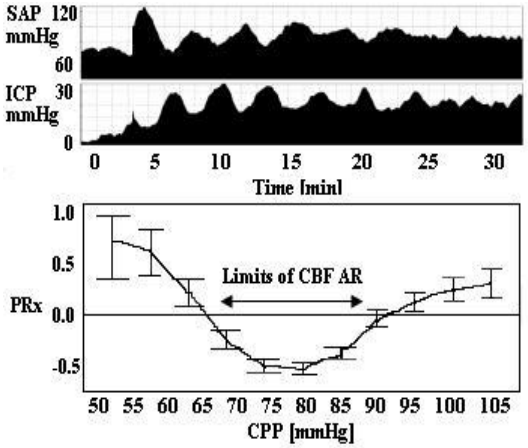

Figure 2. Detection of the limits of CBF AR from the pressure-reactivity index (PRx). In this example. AR is preserved for CPP between 65 - 90 mmHg (modified from [11]).

2. Materials and methods

REG-based estimates of the state and lower limit of CBF AR were compared with the method based on the pressure-reactivity index (PRx) and visual assessment by an expert in anesthetized pigs (N=13) and rhesus macaques (N=8) during the terminal phase of experimental exsanguination. Exsanguination is chosen as a model for CBF AR assessment as it causes SAP to gradually lower and cerebral arteries to maximally dilate until the autoregulation is exhausted. REG and ICP were measured concurrently (and *invasively*) in pigs, with the goal to establish direct correspondence between the REG- and ICP-based assessments of CBF AR. The study on monkeys aimed, on the other hand, to assess the utility of non-invasive REG recordings for evaluation of CBF AR.

SAP was measured with a micro-tip pressure transducer (Millar Instruments, Houston, TX) inserted into femoral artery and connected to the Digi-Med Pressure Analyzer, (Micro-Med, Louisville, KY). ICP in pigs was recorded with an intraparenchymal transducer (ICP Express; Codman, Raynham, MA). REG was acquired with intracerebral needle electrodes in pigs and surface (noninvasive) electrodes in macaques using bipolar systems (OTE Galileo, Italy and Cerberus, Quintlab, Hungary). All signals were digitized at 200Hz. SAP and ICP were averaged using a 10-second window, and REG was differentiated, rectified, integrated and time-averaged in order to remove fluctuations and derive the trend signals (tSAP, tICP, tREG) that capture the aforementioned slow oscillations [8 - 10].

Automated PRx- and REGx-based assessment of autoregulation was performed in MATLAB R2008 software (Natick, MA). PRx [10] and REGx [11] were computed by correlating tSAP with the tICP and tREG signals, respectively, using a 5-minute window that was slid along the signals in 1-minute steps. In accord with [10], the automated ICP and REG-based methods qualified CBF AR in each recording as impaired (-) if PRx or REGx were above 0.2 during at least half of the recording time. Distribution of the PRx and REGx indices were analyzed as a function of the averaged SAP signal (as depicted in Figure 2), and the lower limit of CBF AR was determined as the lowest SAP level for which the mean value of pertinent correlation index was still negative. The expert used the WRAIR DataLyser software package to view the signals, assess the state of CBF AR, and determine its lower limit if CBF AR was considered active (+).

3. Results

1.1. Invasive REG vs. ICP-based and expert assessment in pigs

The PRx- and REGx-based classifications of the CBF-AR status were identical in all 13 animals (**Table** 1), and there was a close agreement between the PRx- and REG-based estimates of the lower limit of CBF AR, when the latter was determinable (n= 7; PRx-based: 58.5 ± 6.1 mmHg; REGx-based: 54.3 ± 6.4 mmHg). The pooled point-to-point correlation between the REGx and PRx values was significant (Spearman r = 0.44, $p<0.001$), but the observed degree of variability of the short-term (5-minute) estimates of both indices warrants additional studies with the focus on selectivity of this approach under various conditions. The automated evaluation of the CBF AR status agreed with the expert's assessment in all but one animal. REGx-based estimates of the lower limit of CBF AR were, however, lower than the values determined by the expert (61.4 ± 10.5 mmHg, p=0.11).

Table 1. CBF AR evaluation in pigs.

Pig	**State of CBF AR**			**Lower limit [mmHg]**		
No.	Exp	PRx	REGx	Exp	PRx	REGx
03	+	+	+	68	63	63
04	+	+	+	54	68	58
08	+	+	+	79	53	58
09	+	+	+	51	n/d[a)]	48
12	+	+	+	56	58	58
13	+	+	+	60	57	48
10	+	+	+	n/d[b)]	n/d[b)]	n/d[b)]
06	-	+	+	n/a[c)]	52	47
11	-	-	-	Cannot be determined if CBF AR is lost		
07	-	-	-			
01	-	-	-			
02	-	-	-			
05	-	-	-			

Table 2. CBF AR evaluation in macaques.

Monkey	**State of AR**		**Lower limit**	
No.	Exp	REGx	Exp	REGx
02	+	+	50	58
05	+	+	70	62
07	+	+	55	62
08	+	+	35	38
01	-	-	Cannot be determined if AR is lost	
03	-	-		
04	-	-		
06	-	-		

[a)] Not determinable as 0.0 < PRx <0.2 throughout most of the record.
[b)] PRx and REGx <0 throughout the record.
[c)] Expert assessment not attempted.

1.2. Non-invasive REG vs. expert assessment in monkeys

There was a perfect agreement of the REG-based and expert classifications of the state of CBF AR (**Table** 2), and a close agreement between the expert and REGx-based estimates of the lower limit of AR, when the latter was determinable (n = 4; expert: 52.5 ± 14.4 mmHg; REG: 55.0 ± 11.9 mmHg).

4. Conclusion

The results obtained in pigs concur to the findings (in rats) that amplitude changes in the intracranial REG signal reflect changes in cerebral vascular resistance [9], and further strengthen the hypothesis that the REGx index could substitute the PRx index in the assessment of CBF AR [11]. The results

from monkeys represent, on the other hand, the first demonstration that surface REG recordings and the respective *noninvasive* correlation index can be used for the assessment of the state and limits of CBF AR. This is important for affirmation of the method in the light of the decades-old debate about the relevance of extracranial impedance measurements in evaluation of intracranial phenomena [12]. Additional studies are, however, warranted in animal models, human volunteers and clinical populations to quantify sensitivity and selectivity of the automated, surface REG-based evaluation of CBF AR during physiological CBF manipulations, hemorrhage, brain blast injury and stroke.

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